IAA Journal of Scientific Research 13(1):135-140, 2026. www.iaajournals.org

©IAAJOURNALS ISSN: 2636-7319

https://doi.org/10.59298/IAAJSR/2026/131135140 IAAJSR:1311

Exosome-Mimicking Nanoparticles: Next-Generation Therapeutics for Obesity-Induced Type 2 Diabetes

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ABSTRACT

Obesity-induced type 2 diabetes (T2D) emerges from sustained nutrient surplus, low-grade inflammation, and interorgan crosstalk that locks adipose tissue, liver, skeletal muscle, and pancreatic islets into insulin-resistant states. Exosomes - 30–150 nm extracellular vesicles are central messengers in this network, shuttling microRNAs, proteins, and lipids that remodel recipient cell programs. Native exosomes show therapeutic promise but face practical barriers: heterogeneous composition, low yield, batch variability, and concerns about immunogenicity and scalability. Exosome-mimicking nanoparticles (EMNs) seek to capture exosomal advantages like biophysical architecture, ligand-guided tropism, and efficient cellular entry while enabling reproducible, cGMP-ready manufacture. Built from lipids, polymers, or membrane-cloaked hybrids, EMNs can be engineered for organ selectivity and loaded with small molecules, peptides, RNAs, and genome editors to recalibrate insulin signaling, mitochondrial function, and inflammatory tone. Rational design uses exosomal lipidomics, integrin-mimetic motifs, and glycoconjugates to improve uptake and endosomal escape, while tuning size, stiffness, and surface chemistry to navigate the reticuloendothelial system characteristic of obesity. Preclinical studies in diet-induced models demonstrate improvements in hepatic steatosis, adipose inflammation, skeletal muscle oxidative metabolism, and β-cell resilience, often at lower doses than free drugs. Translation now hinges on standardized potency assays, biodistribution profiling in metabolically diseased hosts, long-term safety, and industrial control of critical quality attributes. This review integrates pathophysiologic rationale, design rules, targeting strategies, efficacy readouts, and manufacturing considerations to chart a practical route for first-in-human evaluation of EMNs in obesity-driven T2D.

Keywords: exosome-mimicking nanoparticles, obesity, type 2 diabetes, targeted RNA delivery, metabolic inflammation

INTRODUCTION

Obesity and T2D are not merely co-occurring conditions; they are mechanistically entwined through disturbed nutrient handling and chronic inflammation. As adipocytes enlarge, regional hypoxia and endoplasmic reticulum stress recruit and reprogram resident immune cells, promoting cytokine production and extracellular matrix remodeling[1–3]. Lipids spill into liver and skeletal muscle, where ceramides and diacylglycerols blunt insulin receptor signaling and impede GLUT4 trafficking. β-cells initially compensate by increasing insulin output, but persistent glucolipotoxicity drives oxidative stress, unfolded protein response activation, and ultimately functional decline or dedifferentiation[4–6]. Superimposed on this biochemistry is a dense web of interorgan messengers, adipokines, myokines, hepatokines, bile acid signals, microbial metabolites, and extracellular vesicles that broadcast metabolic status across tissues [7].

Exosomes sit near the center of this web. Formed within multivesicular bodies and released upon fusion with the plasma membrane, exosomes are enriched for tetraspanins, specific lipids, and selectively packaged nucleic acids. In obesity, adipose-derived vesicles carry cargo that dampens insulin signaling in the liver and muscle, while hepatocyte vesicles influence gluconeogenesis, lipogenesis, and stellate cell activation. Myocyte vesicles can promote or hinder adipose browning depending on activity state, and islet vesicles modulate immune surveillance and β-cell fate[8–11]. Their natural tissue tropism, partly encoded by integrins, glycans, and membrane composition, makes exosomes appealing blueprints for therapeutics that must reach multiple, distinct cell types.

However, turning native exosomes into medicines remains challenging. Isolating standardized populations at a clinical scale is difficult; cargo composition varies with source cell biology and culture conditions, and safety oversight is complicated by residual nucleic acids or proteins of unknown function[12]. These limitations have catalyzed interest in exosome-mimicking nanoparticles. EMNs borrow exosomal dimensions, curvature, and biochemical cues but are assembled from well-defined lipids, polymers, or hybrid shells, often decorated with peptides, aptamers, or purified membrane proteins[8, 13, 14]. Unlike traditional nanoparticles that rely mainly on PEGylation for stealth and receptor antibodies for targeting, EMNs aim for "biological stealth" through exosome-like lipidomics and self-signals, while preserving modularity to swap cargo and ligands for different disease endotypes.

For obesity-induced T2D, EMNs offer a vehicle to intervene at several levels: dampening adipose inflammation, restraining hepatic lipogenesis, restoring muscle oxidative capacity, and safeguarding β-cell identity[15]. They can carry siRNAs against phosphatases that brake insulin signaling, mRNAs that boost mitochondrial biogenesis, peptides that activate incretin pathways, or small molecules that toggle AMPK and mTOR. By combining multiple payloads in one vesicle, EMNs can deliver polypharmacology to the exact cells that maintain hyperglycemia, potentially lowering the dose and widening the therapeutic index[15]. Engineering choices size in the 60–120 nm window, cholesterol and sphingomyelin content for membrane order, ionizable lipids for endosomal escape, zwitterionic or CD47-mimetic features to evade complement, are guided by the altered vascular permeability and heightened macrophage activity typical of obesity[16].

The field now needs a unifying framework that links design parameters to biodistribution and functional outcomes across organs, benchmarks EMNs against standard-of-care drugs and native exosomes, and maps a cGMP path with measurable critical quality attributes. The following sections provide such a framework: the biological rationale for biomimicry, the engineering toolbox, cargo strategies, targeting logic in metabolically diseased tissues, evidence from preclinical models, and the translational path from process analytics to first-in-human trials.

2. Biomimicry Rationale and the Pathophysiology Interface

Metabolic disease behaves like a network disorder in which signals propagate across tissues through vesicular traffic. Adipose tissue expansion increases necrotic adipocytes and crown-like structures, with macrophages releasing vesicles that carry microRNAs repressing insulin pathway nodes in hepatocytes and myocytes[17]. Conversely, hepatocyte vesicles modulate adipose lipolysis and sensitize stellate cells, feeding forward inflammation and fibrosis. Myocyte vesicles reflect activity state; exercise enriches cargo that encourages adipose browning and improves hepatic lipid handling, whereas inactivity does the opposite[17]. EMNs transpose this logic into drug carriers. By matching exosomal lipid order, curvature, and surface motifs, EMNs exploit the same endocytic and fusogenic pathways, increasing uptake without relying solely on high-affinity antibodies that can be masked by protein coronas in vivo.

Biomimicry also addresses pharmacokinetic hurdles. In obesity, the reticuloendothelial system is activated, accelerating clearance of conventional nanoparticles[18, 19]. EMNs that present self-like signals and exosome-style glycans reduce opsonization and complement activation, extending circulation long enough to access inflamed adipose depots and fenestrated hepatic sinusoids. Critically, EMNs enable combination therapy. Metabolism is governed by intertwined axes like AMPK–mTOR, insulin/IGF signaling, NF-κB–NLRP3, and bile acid receptor pathways[20]. Delivering synergistic payloads within a familiar biological envelope makes it plausible to reset network behavior rather than toggle single nodes.

2. Engineering Exosome-Mimicking Nanoparticles: Materials and Fabrication

EMNs span lipid, polymer, and hybrid architectures. Lipid systems include exosome-like liposomes rich in sphingomyelin and cholesterol for membrane order, and ionizable lipid nanoparticles optimized for RNA with phosphatidylserine to encourage natural uptake. Polymer vesicles formed from PEG-PLGA or poly(β-amino esters) add mechanical robustness and tunable release[21–24]. Hybrids combine a lipid leaflet for fusion competence with a polymer scaffold for stability. Membrane-cloaked EMNs wrap synthetic cores with purified cell or exosomal membranes, conferring native tetraspanins and integrins that guide tropism.

Scalable fabrication favors gentle, continuous-flow methods. Microfluidic mixing yields tight size distributions and reproducible encapsulation. Thin-film hydration followed by controlled extrusion remains useful for lipids, whereas nanoprecipitation and double emulsion techniques serve polymers. Post-assembly surface engineering introduces ligands via click chemistry or maleimide–thiol coupling, while detergent-assisted reconstitution inserts purified proteins with controlled orientation[25]. Quality control centers on mean size (≈60–150 nm), low polydispersity, balanced zeta potential, ligand density per particle, cargo loading efficiency, endotoxin burden, and sterility[26, 27]. Serum stability and protein corona profiling anticipate in vivo performance, with zwitterionic coatings or pre-adsorbed opsonin shields used to preserve targeting.

3. Cargo Selection and Loading for Metabolic Reprogramming

EMNs are agnostic to modality. Small molecules such as AMPK activators, ACC inhibitors, DGAT2 antagonists, and mitochondrial uncouplers can be bilayer- or core-loaded depending on lipophilicity[28]. Peptide and protein cargos GLP-1 analogs, dual/triple incretin mimetics, adiponectin receptor agonists benefit from protease protection and tissue-directed deposition. Nucleic acids expand the palette: siRNAs silencing PTP1B or SOCS3, antisense oligos reducing hepatic lipogenesis, and microRNA mimics that restore insulin

pathway tone. mRNAs encoding PGC-1α variants or antioxidant enzymes upgrade mitochondrial function in muscle and adipose[29, 30]. For durable edits, EMNs can deliver CRISPR base or prime editors to hepatocyte targets relevant to dyslipidemia and insulin resistance, with ionizable lipids promoting endosomal escape and membrane cloaks blunting innate sensing.

Loading uses passive encapsulation during assembly, remote loading via pH gradients for weak bases, polyelectrolyte complexation for RNAs, and affinity tag strategies for oriented protein insertion[31]. Stimuli-responsive components, pH-labile lipids, redox-cleavable linkers, and enzyme-degradable polymers synchronize release with inflamed microenvironments. Patient endotyping guides payload choice: in steatohepatitis-dominant disease, lipogenesis suppression and β-oxidation support take priority; in adipose-inflammation phenotypes, anti-NLRP3 and macrophage-reprogramming cargos lead[32–35]. Pharmacodynamic assays, like AKT and ACC phosphorylation, oxygen consumption rates, mtDNA copy number, glucose and insulin tolerance tests, anchor potency to mechanism.

4. Targeting Strategies and Biodistribution in Obesity-Induced T2D

Achieving the right cell address requires a layered design. Adipose targeting employs peptides for prohibitin or neuropilin-1, as well as motifs discovered by in vivo phage display that bind inflamed endothelium typical of obese depots. Brown and beige fat can be engaged through β3-adrenergic receptor-interacting ligands or UCP1-adjacent motifs[36]. The liver is naturally accessible; promoting apolipoprotein E adsorption enhances LDL receptor-mediated hepatocyte uptake, while GalNAc clusters drive asialoglycoprotein receptor internalization. Vitamin A directs stellate cell uptake; mannose engages Kupffer cells[36]. Skeletal muscle, more difficult to penetrate, benefits from reduced particle stiffness, transferrin or insulin receptor ligands, and dosing under conditions that transiently increase perfusion. For β-cells, GLP-1 receptor fragments or SUR1-binding peptides enhance islet deposition without compromising microcirculatory flow.

Particle size around 80–120 nm usually balances renal retention with tissue penetration. Zwitterionic or CD47-mimetic surfaces mitigate complement activation in obesity. Biodistribution is quantified with radiotracers or MS-detectable lipids and interpreted with physiologically based pharmacokinetic models that account for inflamed tissue permeability and expanded lipid compartments[37]. Repeated dosing can trigger accelerated clearance; alternating stealth chemistries or using membrane-cloaked variants reduces this risk. Importantly, successful targeting culminates in productive intracellular routing cytosolic delivery for RNAs, mitochondrial localization for energetics modulators, or nuclear access for editors since mere uptake is not equivalent to efficacy.

5. Preclinical Efficacy and Mechanistic Insights

Across diet-induced obesity and genetic models, EMNs outperform matched free drugs by concentrating payloads where they matter. Adipose-homing EMNs delivering anti-inflammatory microRNAs reduce crown-like structures, skew macrophages toward reparative phenotypes, and restore insulin-stimulated glucose uptake[38]. Hepatocyte-directed EMNs carrying siRNAs against lipogenic enzymes lower hepatic triglyceride content, blunt de novo lipogenesis, and improve insulin sensitivity with parallel reductions in aminotransferases[38]. In skeletal muscle, EMN-mRNA programs that elevate PGC-1α increase mitochondrial density and fatty acid oxidation, translating to better whole-body glucose disposal. β-cell-targeted EMNs that deliver antioxidant enzymes or identity-preserving microRNAs maintain glucose-stimulated insulin secretion under glucolipotoxic stress and limit dedifferentiation markers[39].

Mechanistically, EMNs ease inflammatory brakes on insulin signaling via NF-κB and NLRP3 dampening, while delivered RNAs and small molecules re-balance kinase–phosphatase networks and GLUT4 trafficking. AMPK activation and SREBP-1c suppression in hepatocytes redirect substrate flux from lipogenesis to oxidation; mitochondrial payloads reduce ROS propagation that otherwise sabotages insulin action[40]. Synergistic, co-loaded regimens often achieve glycemic benefits comparable to incretin or SGLT2 therapies but with broader effects on steatosis and fitness endpoints and with lower systemic exposure. Some studies report durable improvements after dosing cessation, consistent with network reprogramming rather than transient agonism[40]. The field now needs harmonized endpoints, dose–exposure–response maps, and head-to-head comparisons across EMN classes to illuminate phenotype-matched applications.

6. Safety, Manufacturability, and Translational Outlook

Safety considerations mirror and extend those for lipid nanoparticles and biologics: infusion reactions, complement activation–related pseudoallergy, immunogenicity of PEG or membrane proteins, off-target organ exposure, and, for genome editors, genotoxicity and bystander edits[41]. Biomimetic lipids, zwitterionic shells, and rigorous endotoxin control minimize innate activation. High-fidelity editors, transient expression windows, and strict tissue targeting mitigate editing risk. Because obesity heightens reticuloendothelial activity and alters complement, toxicology should be performed in metabolically diseased models and should include repeated-dose studies that probe accelerated blood clearance[41].

Industrialization leans on continuous-flow microfluidics for scalable assembly with in-line size metrology, coupled to membrane cloaking protocols with orientation control for inserted proteins. Critical quality attributes like size, PDI, zeta potential, lipid/protein composition, ligand density, cargo encapsulation, residual solvent, endotoxin, sterility must be tied to potency assays that reflect mechanism, such as insulin-stimulated glucose uptake in myotubes, suppression of hepatic lipogenesis, macrophage cytokine profiles, and biodistribution

metrics in obese animals[42]. Stability programs establish shelf life with cryoprotectants and lyophilization where feasible. Early regulatory dialogue should fix identity and potency assays, biodistribution expectations in impaired renal and fatty liver states, and release specifications. Initial clinical studies may focus on hepatocyte- or adipose-targeted RNA cargos with rapid pharmacodynamic readouts, progressing to combination payloads and, ultimately, adaptive, endotype-guided EMN platforms integrated with circulating exosomal biomarkers.

CONCLUSION

Exosome-mimicking nanoparticles bring the logic of physiological vesicle traffic to the engineering bench, offering a modular, scalable way to deliver polypharmacology into the precise tissues that sustain obesity-induced T2D. By emulating exosomal membrane composition and tropism while retaining synthetic control, EMNs can overcome the clearance, targeting, and cargo-stability limitations that have constrained both native exosomes and conventional nanocarriers. Preclinical data support multi-organ benefits less adipose inflammation, reduced hepatic steatosis, restored muscle oxidative capacity, and preserved β-cell function at exposures that promise wider therapeutic windows. The path to patients now depends on disciplined translational work: standardized potency assays that reflect mechanism across tissues, biodistribution and safety testing in metabolically diseased hosts, and cGMP processes that lock critical quality attributes to clinical performance. If these pieces align, EMNs could shift diabetes care from glucose management toward durable network reprogramming, complementing or potentiating incretin and SGLT2 therapies in a precision, endotype-guided manner.

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CITE AS: Muhindo Edgar (2026). Exosome-Mimicking Nanoparticles: Next-Generation Therapeutics for Obesity-Induced Type 2 Diabetes. IAA Journal of Scientific Research 13(1):135-140. https://doi.org/10.59298/IAAJSR/2026/131135140